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There are several errors in the meta-analysis on vitamin C and post-operative atrial fibrillation (POAF) by Hu et al. (1).

Hu et al. stated in their methods that "studies that met the following criteria were included: (1) randomized controlled trials (RCTs) of adult … patients who underwent cardiac surgery; (2) patients randomly assigned to receive vitamin C or placebo … Any studies of non-randomized designs … were excluded" (1, p. 59). However, Hu included the study by Carnes et al. although that was not an RCT, instead "an age- and gender-matched control group (not receiving ascorbic acid) was retrospectively selected" (2, p. 3). In addition, Hu did not include the data of two so far largest vitamin C and POAF trials that found no effect of vitamin C against POAF and therefore remained unpublished, leading to publication bias (3). Hu claimed that "funnel plots showed no evidence of publication bias" (p. 60), but the existence of those 2 unpublished large negative trials obviously proves that there is publication bias.

Hu et al. calculated that the effect of vitamin C on POAF was OR = 0.47. However, Altman (4) pointed out that "the odds ratio [OR] should not be interpreted as an approximate relative risk [RR] unless the events are rare in both groups (say, less than 20-30%)". In Hu's Fig. 2, the lowest incidence of POAF in the placebo groups was 19%, and 6 out of 8 studies had incidence of POAF over 30% in their placebo groups (1). In such a case the OR does not properly approximate RR. Instead, the OR can substantially exaggerate the effects for common outcomes (4). Thus, Hu's OR = 0.47 does not indicate that vitamin C reduced the risk of POAF by 53%. Hu should have calculated the effect of vitamin C on the RR scale instead.

In their Fig. 4, Hu et al. stated that the standard devation (SD) of the mean duration of ICU stay in the vitamin C group was 24.9 hours in the trial by Colby et al. (5). However, Colby reported in their Table 1 and text that the SD for the duration of ICU stay was 249.9 hours in their vitamin C group, i.e. 10 times greater than Hu claimed. Evidently, such a big error leads to a large error in the pooled estimate of effect, but also generates great exaggeration of the heterogeneity between the included trials. Hu wrote "compared with placebo group, vitamin C administration was not associated with any length of stay, including in the ICU" (1, p. 60). However, I calculated that there was strong evidence from 10 RCTs that vitamin C shortened the ICU stay in the POAF trials by 7.4% (P = 0.002)(3). This divergence in conclusions seems to be largely caused by Hu's 10-fold error in the SD value of the Colby trial mentioned above.

Although the general conclusion of Hu et al. that vitamin C has some efficacy against POAF is consistent with trial reports, there is very strong evidence of heterogeneity in the effect (3), even though Hu claimed that there was "no significant heterogeneity (I^2 = 44%; P = 0.09)" (1, p. 60). High level heterogeneity has important implications as it guides further research. Five trials in the USA found no benefit, discouraging further research in the USA (3). However, positive findings in less wealthy countries suggest that the effect of vitamin C should be further studied in such countries (3).

Provenance and peer review
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